PATENT
Attorney Docket No. UCSD-04765

REMARKS

A. Restriction Requirement

In a prior Office Action, the Examiner restricted the claims into three groups as follows:

Group I: Claims 1-25 and 43-59;

Group II: Claims 26-29 and 34-42; and

Group III: Claims 30-33.

A further restriction of the following three species was also imposed for each of Groups I (Claims 1-9, 11-25, 43-51, 54-59), and II (Claims 34-39, 41-42):[1]

i) katanin and the p60 subunit of katanin;

ii) XKCM1; and

iii) OP18 polypeptide.

Applicants previously elected Group I (*i.e.*, Claims 1-25 and 43-59) and species (i) (*i.e.*, katanin and the p60 subunit of katanin), with traverse.

Applicants note the Examiner's remark in the instant Office Action, that "the traversal of the restriction of species i-iii is persuasive and the Examiner has rejoined the species."[2]

B. Status of the Claims

Claims 1-59 are pending in the present application.

1. Relationship of claims in the instant application to claims in related applications

i. Claims 1-16

Claims 1-16 in the instant application include within their scope the matter claimed in Claims 1-16 of abandoned Application No. 09/724,887 (our docket No. UCSD-04865).

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[1] Office Action, page 3.

[2] Paper No. 16, page 2, item 2.

ii. Claims 17-25

Claims 17-25 in the instant application include within their scope the matter claimed in Claims 17-25 of abandoned Application No. 09/724,598 (our docket No. UCSD-04885).

iii. Claims 43-46 and 48-85:

Claims 43-46 and 48-85 the instant application include within their scope the matter claimed in Claims 43-46 and 48-85 of abandoned Application No. 09/724,596 (our docket No. UCSD-04867). The reasons and support for the instant Claims 43-46 and 48-85 are the same as those discussed in Applicants' response that was mailed on 11/27/02 in application serial No. 09/724,596 (our docket No. UCSD-04867).

iv. Claims 86-111:

Claims 86-111 in the instant application include within their scope the matter claimed in Claims 43-51 and 55-71 of abandoned Application No. 09/724,595 (our docket No. UCSD-04868). In particular, new Claims 86-111 do not recite that the agent alters microtubule "severing", but instead recite that the agent alters microtubule polymerization and/or depolymerization. Support for new claims 86-111 is the same as that discussed in Applicants' response that was mailed on 10/21/02 in application serial No. 09/724,595 (our docket No. UCSD-04868).

v. Claims 112-124:

Claims 112-124 in the instant application include within their scope the matter claimed in Claims 51 and 55-66 of abandoned Application No. 09/724,602 (our docket No. UCSD-04869). In particular, new Claims 112-124 do not recite that the agent alters microtubule "severing", but instead recite that the agent alters microtubule polymerization and/or depolymerization, and that the microtubule depolymerizing protein comprises stathmin. Support for new Claims 112-124 is the same as that discussed in Applicants' response that was mailed on 10/21/02 in application serial No. 09/724,602 (our docket No. UCSD-04869).

2. Amendments:

Claim cancellations and amendments were made to better define preferred embodiments of the invention, notwithstanding Applicants' belief that the cancelled and unamended claims would have been allowable, without acquiescing to any of the Examiner's arguments, and without waiving the right to prosecute the unamended (or similar) claims in another application, but rather for the purpose of furthering Applicants' business goals and expediting the patent application process in a manner consistent with the PTO's Patent Business Goals (PBG).[3] None of the amendments to the claims is related to the statutory requirements of patentability.

In particular, Claims 26-42 have been cancelled in response to a restriction requirement without prejudice to their renewal in a future application. Applicants' cancellation of Claims 26-42 does not narrow the scope of any of the claims because cancellation of non-elected claims in not related to a statutory requirement for a patent, but rather is related to the Patent Office's convenience for organizing searches.

Claims 1, 16, 25, 43, 58, and 59 have been amended to recite a "test" agent. Also, Claim 17 has been amended to recite a test "agent" instead of test "compound" to provide antecedent basis for this term, which appears in dependent Claims 19 and 20. Support for the term "test agent" is found in the teaching:

> "The term "test agent" refers to an agent that is to be screened in one or more of the assays described herein. The agent can be virtually any chemical compound. It can exist as a single isolated compound or can be a member of a chemical (e.g., combinatorial) library. In a particularly preferred embodiment, the test agent will be a small organic molecule."[4]

Claims 1 and 17 have also been amended to recite "at least one protein selected from the group consisting of" a microtubule severing protein and microtubule deplymerizing protein. Support is found in the specifcation's disclosure that the modulators " . . . provide novel lead compounds for the development of highly specific inhibitors for depolymerizing **and/or** microtubule severing protein families and subfamilies, thus allowing for precise

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[3] 65 Fed. Reg. 54603 (September 8, 2000).

[4] Sp cification, page 10, lines 27-30.

chemical intervention."[5] Also, the Specification teaches ". . . assaying the impact of a test agent on microtubule polymerization, **and/or** depolymerization, **and/or** severing."[6]

Claims 2 and 48 have been amended by inserting the term "4'-6-diamidino-2-phenylindole", which is equivalent to the originally-recited term "DAPI" as supported by Heusele *et al.* (1987) Eur. J. Biochem. 165: 613-620, a copy of which was previously submitted as reference # 104 in PTO-1449, and which is referred to in the Specification as follows:

> "In another embodiment, the state of microtubule polymerization can be determined by changes in fluorescence of DAPI stained microtubules. It has been shown that DAPI fluorescence intensity is higher when this dye is bound to polymerized versus free tubulin (Heusele et al. (1987) Eur. J. Biochem. 165: 613-620)."[7]

Claim 9 has been amended by adding the term "stathmin" which is equivalent to the recited term "OP18" as supported by the Specification and references cited therein:[8]

> "Another microtubule depolymerizing motor protein suitable for use in the methods of this invention is OP18, also called stathmin or stathmin/op18. OP18 is described in detail by Gradin et al. (1998) J. Cell Biol., 140(l):131-141, by Andersen et al. (1997) Nature, 389(6651):640-643, by Larsson et al. (1997) Mol. Cell. Biol., 17(9):5530-5539, and by Belmont et al. (1996) Cell, 84(4):623-631."[9]

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[5] Specificaiton, page 15, lines 17-20.

[6] Specification, page 27, lines 18-22.

[7] Specification, page 27, lines 9-11.

[8] Gradin *et al.* (1998) *J. Cell Biol.*, 140(l):131-141, IDS reference #91, page 131, column 2 states: "Op18 has been given many names in the literature (*e.g.*, p19-19K, metablastin, prosolin, and stathmin) . . ."; Andersen *et al.* (1997) *Nature*, 389(6651):640-643, IDS reference #92, page 643, column 1, discloses "*Xenopous* Stathmin/Op18 cloning and expressions;" Larsson *et al.* (1997) *Mol. Cell. Biol.*, 17(9):5530-5539, IDS reference #93, Abstract, discloses "Oncoprotein 18 (Op18; also termed p19, 19K, metablastin, stathmin, and prosolin) . . .;" Belmont *et al.* (1996) *Cell*, 84(4):623-631, IDS reference #94, paragraph bridging pages 627-628, page 629 under "Purification" and "Protein Sequencing," discloses purification and sequence analysis of Op18/stathmin.

[9] Specification, page 25, lines 26-30.

Claim 9 has also been amended by adding th term "*Xenopus* kinesin central motor 1" which is equivalent to the recited term "XKCM1" as disclosed in the Specification, page 25, lines 19-24.

Claims 9 and 10 have been amended to provide further clarity by adding the recitation "polypeptide" after each of katanin, p60 subunit of katanin, XKCM1 and op18.

Claims 11 and 53 has been amended by incorporating the limitations of cancelled Claim 26. This is not a narrowing amendment since it paraphrases the originally-filed reference to Claim 26.

Claim 17 has been amended by replacing "a microtubules" with "a microtubule" to correct a grammatical error.

Claims 21, 25, 55 and 59 have been corrected to delete a period from the middle or end of the claim to conform to proper claim format.

Claim 43 has been amended by incorporating the limitations of cancelled Claim 47 to recite specifically preferred labels, such as DAPI, ANS, bis-ANS, NPN, DCVJ, ruthenium red, and cresol violet. Support for the full term for DAPI is the same as that discussed above with respect to amendment of Claims 2 and 48. Support for the full terms for ANS, bis-ANS, and NPN is on page 27, lines 23-26 which teaches:

> "Labels that can be used include, but are not limited to anilinonapthalene sulfonate (ANS) (e.g., Molecular Probes Catalogue Nos: A-47, A-50, T-53, etc.), bis-ANS (Molecular Probes Catalogue No: B-153), N-phenyl-l-naphthylene (NPN) (Molecular Probes Catalogue No: P65), DCVJ (Molecular Probes Catalogue No: D-3923), ruthenium red, and cresol violet."

Additional support for the full name [i.e., 4-(dicyanovinyl)julolidine] of the term "DCVJ" is in attached Tab 3, which shows the full name of DCVJ in the Molecular Probes Catalogue No: D-3923 that is referred to by the immediately preceding sentence from the Specification.

Claims 43, 50, 51, and 59 have also been amended by cancelling the recitation that the agent alters microtubule "polymerization or depolymerization" and that the protein is XKCM1 or OP18 polypeptide.

Claim 44 has been amended to recite proper Markush language.

Claim 48 has been amended to depend from Claim 43 instead of cancelled Claim 47.

Claim 52 has been amended by cancelling the recitation that the microtubule severing protein is "a katanin" to avoid potential duplication of amended Claim 51.

Claim 55 has been amended by deleting the period on line 2, and by cancelling the recitation "each reaction mixture comprising a distinct and distinguishable domain of said array." This is not a narrowing amendment.

Claim 58 has been amended to correct a grammatical error by replacing "one of" with the term "comprises." Support is found in the Specification, page 4, lines 1-3.

Claim 59 has been amended by deleting a period at the end of the claim.

New Claims 60-85 have been added to better describe one embodiment of the invention. In particular, support for Claims 60-72's recitation of providing and contacting with "an isolated polypeptide having microtubule severing activity and comprising a katanin p60 subunit" and also for Claims 73-85's recitation of providing and contacting with "an isolated katanin p60 subunit" is found, for example, in the Specification, page 25, lines 12-13 which teaches that "the assays of this invention can be practiced either with the heterodimeric katanin or with a p60 subunit alone." Support for Claims 61-72 and 74-85 is found, for example, in the originally-filed Claims 44-59.

New Claims 86-111 have the same support as that for Claims 43-51 and 55-71 of application serial No. 09/724,595 (our docket No. UCSD-04868) as discussed in Applicants' response that was mailed on 10/21/02 in application serial No. 09/724,595.

New Claims 112-124 have the same support as that for Claims 51 and 55-66 of application serial No. 09/724,602 (our docket No. UCSD-04869) as discussed in Applicants' response that was mailed on 10/21/02 in application serial No. 09/724,602.

C. Information Disclosure Statement

The Examiner indicated that "references numbered 52-57, 105 and 149 have not been considered," and that "Applicants should supply the dates in which the references were published."[10] Enclosed is a supplemental Information Disclosure Statment and form PTO-1449 showing the dates of the references. Accordingly, Applicants respectfully request consideration of reference numbers 52-57, 105 and 149.

[10] Paper No. 16, item 4.

D. Objection To the Specification

The Specification was objected to because of typographical errors, and the presence of colons or square boxes after numbers. In view of the extensive nature of the typographical and grammatical corrections, which appear on almost every page of the Specification, and since the Examiner indicated that a substitute specification in related applications (for example, Application Serial Nos. 09/724,596; 09/724,595; and 09/724,602) would overcome this objection, Applicants enclose the following:

(1) A marked-up copy of the substitute Specification (excluding the Sequence Listing, Claims, Abstract and Figures) (Tab 1, pages 1-60) pursuant to 37 C.F.R. § 1.125(b)(2), showing the matter which was added and deleted from the **originally-filed** Specification, as well as the changes made by Applicants in an Amendment mailed to the Office on June 21, 2001. Strike-through shows deleted matter, and underling shows added matter; and

(2) A clean copy of the substitute Specification (excluding the Sequence Listing, Claims, Abstract and Figures) without markings as to amended material (Tab 2, pages 1-59) pursuant to 37 C.F.R. § 1.125(c). The clean substitute specification includes no new matter.

These amendments do not introduce new matter.

E. Objections To, And Rejections Of, The Claims:

Applicants note that the Examiner found "Claims 1-25 are free of the art."[11]

However, Claims 1-25 and 43-59 have been objected to and rejected on the following grounds:

1. Claims 17, 21, 25, 55, 58, and 59 have been objected to;

2. Claims 2, 4, 9-12 and 55-59 stand rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness;

3. Claims 43-46 and 49-54 were rejected under 35 U.S.C. §102(b) as being allegedly anticipated by McNally & Vale;

[11] Paper No. 16, page 13, item 22.

4. Claims 43-54 stand rejected under 35 U.S.C. §103(a) for alleged obviousness over McNally & Vale in view of Bonne *et al.*;

5. Claims 43-46 and 49-58 stand rejected under 35 U.S.C. §103(a) for being allegedly obvious over McNally & Vale in view of Balch (U.S. Patent No. 6,083,763);

6. Claims 43-46, 49-54 and 59 have been rejected under 35 U.S.C. §103(a) for alleged obviousness over McNally & Vale;

7. Claims 43-51 and 55-59 have been provisionally rejected for obviousness-type double patenting over claims 43-71 of copending Application No. 09/724,595 (our docket No. UCSD-04868);

8. Claims 43-51 and 55-59 have been provisionally rejected for obviousness-type double patenting over claims 51 and 55-66 of copending Application No. 09/724,602 (our docket No. UCSD-04869);

9. Claims 11-16 have been provisionally rejected for obviousness-type double patenting over claims 11-16 of copending Application No. 09/724,887 (our docket No. UCSD-04865);

10. Claims 43-59 have been provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as claims 43-59 of copending Application No. 09/724,596 (our docket No. UCSD-04867); and

11. Claims 1-10 were provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as claims 1-10 of copending Application No. 09/724,887 (our docket No. UCSD-04865).

Applicants believe that the following remarks traverse the Examiner's objections and rejections of the claims. These remarks are presented in the same order as they appear above.

1. Objection to Claims 17, 21, 25, 55, 58, and 59

Claims 17, 21, 25, 55, 58, and 59 have been objected to on the following four bases.[12]

(a) In Claim 17, the phrase "a microtubules" was found improper. Correction has been made to refer to "a microtubule."

[12] Paper No. 16, page 3, item 6.

(b) Claims 21, 25, 55 and 59 were found to contain a period in the middle of the claim or to lack a period at the end of the claim. Correction has been made.

(c) Claim 58 was found to be missing text. Correction has been made

(d) Claims 18-20, 23 and 24 are objected to for dependency upon rejected claims 17 and 21. In view of the following remarks that overcome the rejection of Claims 17 and 21, the objection to Claims 18-20, 23 and 24 is moot.

2. Rejection of Claims 2, 4, 9-12 and 55-59 under 35 U.S.C. §112, second paragraph

Claims 2, 4, 9-12 and 55-59 stand rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness based on the following three reasons:[13]

(a) The Examiner requested amendment of Claims 2 and 9 because they "contain acronyms, DAPI, XKCM1 and OP18 that are not well known in the art." Applicants have inserted the full names of each of these acronyms into the claims as supported by the Specification (discussed *supra*).

(b) The Examiner required correction of Claim 53 since it references non-elected Claim 26. Claim 53 has been amended by inserting the limitations of Claim 26. This is not a narrowing amendment since it paraphrases the originally-filed reference to Claim 26.

3. Rejection of Claims 43-46 and 49-54 under 35 U.S.C. §102(b) over McNally & Vale

Claims 43-46 and 49-54 were rejected under 35 U.S.C. §102(b) as being allegedly anticipated by McNally & Vale.[14] Applicants respectfully disagree.

The law is clear that "[A]bsence from the reference of any claimed element negates anticipation."[15] Importantly, McNally & Vale does **not** disclose the recited tubulin labels DAPI, ANS, bis-ANS, NPN, ruthernium red, cresol violet, and DCVJ.

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[13] Paper No. 16, page 4, item 8.

[14] Paper No. 16, page 5, item 10.

[15] *Rowe v. Dror,* 42 USPQ2d 1550, 1553 (Fed. Cir. 1997), citing *Kloster Speedsteel AB v. Crucible, Inc.,* 793 F.2d 1565, 1571, 230 USPQ 81, 84 (Fed. Cir. 1986).

Specifically, McNally & Vale discloses the purification of katanin (also referred to as p81-p60) from see urchin egg extracts,[16] and identifying p81-p60 as a microtubule-severing protein. This identification was carried out by incubating fluorescein-labeled and rhodamine-labeled tubulins (in solution, or immobilized on glass)[17] with p81-p60, and recording changes in fluorescence. Importantly, the fluorescence changes observed by McNally & Vale were investigated **only** when tubulins were labeled with **fluorescein or rhodamine**, rather than with any of the recited DAPI, ANS, bis-ANS, NPN, ruthernium red, cresol violet, and DCVJ. Since McNally & Vale does not disclose a limitation of the claims, withdrawal of the rejection of Claims 43-46 and 49-54 is respectfully requested.

Referring to new Claims 60-72, these claims are distinguished from McNally & Vale's methods that do **not** include the recited contacting of labeled tubulin with **both** an isolated polypeptide "comprising a katanin p60 subunit" as well as "a test agent." Rather, McNally& Vale's methods involve contacting labeled tubulin with **only** katanin in the absence of a test agent.

Also, new Claims 73-85 are distinguished from McNally & Vale's methods that do **not** disclose the recited "isolated katanin p60 subunit." Instead, McNally & Vale discloses that the heterodimeric katanin, which contains **both** p81 and p60 subunits, has microtubule severing activity.

With respect to new Claims 86-111, McNally & Vale does **not** disclose the recited agent that alters at least one activity selected from "microtubule **polymerization and depolymerization**" (Claims 86-111), "microtubule **depolymerizing** protein" (Claim 93), "**XKCM1**" (Claim 94). Rather, McNally & Vale discloses the microtubule-**severing** protein **katanin**.

As to new Claims 112-124, McNally & Vale does **not** disclose the recited **stathmin polypeptide** but rather discloses the purification of katanin.

For these reasons, new Claims 60-124 are novel over McNally & Vale.

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[16] McNally & Vale, page 427, column 2.

[17] McNAlly & Vale, page 423, Figure 5; page 427, column 2; and page 428, column 1

4. Rejection of Claims 43-54 under 35 U.S.C. §103(a) over McNally & Vale in view of Bonne *et al.*

Claims 43-54 stand rejected under 35 U.S.C. §103(a) for alleged obviousness over McNally & Vale in view of Bonne *et al.*[18] Applicants respectfully disagree since a *prima facie* case of obviousness is not established. A *prima facie* case of obviousness requires the Examiner to cite to a combination of references which (a) suggests or motivates one of skill in the art to combine the claim elements to yield the claimed combination, (b) discloses all the elements of the claimed invention, and (c) provides a reasonable expectation of success should the claimed combination be carried out. Failure to establish any one of these three requirements precludes a finding of a *prima facie* case and, without more, entitles Applicants to allowance of the claims in issue.[19] Not just one, but all three requirements, are lacking, thus entitling Applicants to withdrawal of this rejection.

i. The References Fail to Disclose All The Claims' Limitations

It is axiomatic for establishing a *prima facie* case of obviousness that "all the claim limitations must be taught or suggested by the prior art."[20] This has not been established.

The Examiner **admitted** that McNally & Vale "do **not** teach that the microtubule of the disclosed method is labeled with 4',6-Diamidino-2-phenylindole (DAPI)."[21] This is not the only deficiency of this reference; as explained above in item E.3., McNally & Vale do **not** teach any of the remaining recited tubulin labels of ANS, bis-ANS, NPN, ruthernium red, cresol violet, and DCVJ. Bonne *et al.* also does **not** disclose these tubulin labels but rather discloses that DAPI is a fluorescent probe that binds to tubulin. Accordingly, a *prima facie* case of obviousness cannot stand with respect to rejected claims 43-54.

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[18] Paper No. 16, page 6, item 12.

[19] MPEP §2143; *See, e.g., Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990); *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).

[20] MPEP 2143.03, citing *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

[21] Paper No. 16, page 6, item 12.

Referring to new Claims 60-72, as explained *supra* in item E.3., **none** of the references discloses contacting labeled tubulin with **both** an isolated polypeptide "comprising a katanin p60 subunit" as well as "a test agent."

As to new Claims 73-85, as explained *supra* in E.3., **none** of the references discloses the recited "isolated katanin p60 subunit."

With reference to new Claims 86-111, neither of the references discloses the recited agent that alters at least one of "microtubule **polymerization and depolymerization**" (Claims 86-111), "microtubule **depolymerizing** protein" (Claim 93), and "**XKCM1**" (Claim 94). As to new Claims 112-124, neither of the references discloses the recited **stathmin** polypeptide. Rather, McNally & Vale discloses the microtubule severing protein katanin, and Bonne *et al.* discloses that DAPI is a fluorescent probe that binds to tubulin.

ii. Motivation To Combine the Elements Is Lacking

A key requirement for a *prima facie* case of obviousness is whether a person skilled in the art would be **motivated** to modify the reference to arrive at the **claimed invention.**[22] In particular,

> "the examiner must show *reasons* that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would *select* the elements from the cited prior art references for combination in the manner claimed."[23] Evidence of a suggestion, teaching, or motivation to modify prior art references "must be *clear and particular*."[24]

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[22] *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988) and *In re Jones*, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992).

[23] (Emphasis added) *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998); *Robotic Vision Systems Inc. v. View Engineering Inc.*, 51 USPQ2d 1948 (Fed. Cir. 1999).

[24] (Emphasis added) *In re Dembiczak*, 175 F.3d 994, 50 USPQ2d 1614 (Fed. Cir. 1999), *citing C.R. Bard*, 157 F.3d 1340 at 1352, 48 USPQ2d at 1232. See, also, *In re Sang Su Lee*, 277 F.3d 1338, 61 USPQ2d 1430 (Fed. Cir. 2002).

The Examiner argued that "one of skill in the art would have been motivated to [utilize DAPI] . . . by the teachings of Bonne because DAPI permits a practitioner to follow the kinetics of polymerization *in vitro*."[25] This argument suffers from at least three problems.

First, the Examiner's argument ignores **all** the limitations of the claimed invention. The claimed invention recites using tubulin that is labeled with one or more of DAPI, ANS, bis-ANS, NPN, ruthernium red, cresol violet, and DCVJ. However, since these labels are **not** disclosed by any of the references, a logical argument cannot be made for a motivation to use them to label tubulin. This precludes establishing a *prima facie* case of obviousness.

Second, the Examiner has failed to consider that Bonne *et al.* **teaches away** from the claimed invention. A teaching away alone can defeat obviousness.[26] Bonne *et al.* teaches that DAPI "is **not** a good probe" under some circumstance because Bonne *et al.*:

> "were **not** able, thus far, to visualize the microtubule network and mitotic spindles in 3T3 fibroblasts either in fixed and permeabilized or unfixed preparations."[27]

In other words, Bonne *et al.*'s **failure** to visualize DAPI-labeled tubulin **teaches away** from, rather than motivates towards, using DAPI-labeled tubulin. This negates a *prima facie* case of obviousness.

Third, the Examiner erroneously equates availability of DAPI-labeled tubulin with obvious. The law is clear that:

> "That which is within the capabilities of one skilled in the art is not synonymous with obviousness."[28]

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[25] Paper No. 16, page 7, first full paragraph, citing Bonne *et al.*, page 2824, column 2, third and fourth paragraphs.

[26] *Winner International Royalty Corp. v. Wang*, 53 USPQ2d 1580, 202 F.3d 1340, 13449 (Fed. Cir. 2000), citing *Gambro Lundia AB v. Baxter Healthcare Crop.*, 110 F.3d 1573, 1579, 42 USPQ2d 1378, 1383 (Fed. Cir. 1997).

[27] (Emphasis added) Bonne *et al.*, page 2824, column 2, third paragraph.

[28] *Ex parte Levengood*, 28 USPQ2d 1300, 1302 (Pat. Bd. Appeals & Interf. 1993), citing *Ex parte Gerlach*, 212 USPQ 471 (Pat. Bd. Appeals & Interf.. 1980). See, also fn. 16 of *Panduit Corp. v. Dennison Mfg. Co.*, 774 F.2d 1082, 1092, 227 USPQ 337, 343 (Fed. Cir. 1985).

At best, the examiner's comment regarding obviousness amounts to an assertion that one of ordinary skill in the relevant art would have been able to arrive at Applicants' invention because he was capable of carrying out **individual** steps among the recited **combination** of steps. This is an inappropriate standard for obviousness.

Based on the above, motivation to combine the references is lacking with respect to rejected Claims 43-54 (and new claims 60-85), thus negating a *prima facie* case of obviousness.

Referring to new Claims 86-111, motivation is also lacking for the additional reason that the references do not disclose the limitation of using the recited agent that alters at least one of "microtubule **polymerization and depolymerization**" (Claims 86-111), "microtubule **depolymerizing** protein" (Claim 93), and "**XKCM1**" (Claim 94). As to new Claims 112-124, neither of the references discloses the recited **stathmin** polypeptide. Since these limitations are **not** disclosed by any of the references, a logical argument cannot be made for a motivation to combine them with labeled tubulin.

iii. A Reasonable Expectation Of Success Is Not Established

A fundamental requisite of establishing a *prima facie* case of obviousness is that there is a reasonable expectation of success in making and using the recited sequences.

> "[T]he reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure."[29]

The Examiner argued that "one of skill in the art would have [utilized DAPI] . . . with a reasonable expectation of success by the teachings of Bonne because DAPI permits a practitioner to follow the kinetics of polymerization *in vitro*."[30]

However, this argument ignores Bonne *et al.*'s **teaching away** from a reasonable expectation of success. As discussed above in item 6.B., Bonne *et al.* teaches that DAPI "is **not** a good probe" since the authors "were **not** able, thus far, to visualize the microtubule network and mitotic spindles in 3T3 fibroblasts either in fixed and permeabilized or unfixed

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[29] *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988) as cited in *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

[30] Paper No. 16, page 7, first paragraph, citing Bonne *et al.*, page 2824, column 2, third and fourth paragraphs.

preparations."[31] Thus, Bonne *et al.*'s **failure** to visualize DAPI-labeled tubulin points to unpredictability rather than to a reasonable expectation of success.

Importantly, Bonne *et al.*'s experiments relate to detecting the fate of tubulin assembly and disassembly in the **absence** of an "agent" that "alters microtubule severing." Thus, nothing in Bonne *et al.* suggests that labeling tubulin with DAPI would **not** adversely affect the recited interaction between tubulin and a test agent.

Bonne *et al.*'s silence on a "reasonable expectation of success" is confirmed by Applicants' surprising results. Under the law, a *prima facie* case of obviousness can be rebutted by the Specification's disclosure that the claimed invention yields unexpected results.[32] The Specification states that:

> "It was a **surprising** discovery of this invention that tubulin, tubulin dimers, tubulin oligomers or microtubules can be labeled with various labels such as DAPI and that **the label does not interfere with the interaction** of various test agents or cytoskeletal associated proteins with the labeled tubulin to a degree that would prevent [*sic.*] assayin the impact of a test agent on microtubule polymerization, and/or depolymerization, and/or severing."[33]

Since the inventors' results were surprising in the face of Bonne *et al.*'s disclosure, the third element of a *prima facie* case of obviousness is absent with respect to rejected claims 43-54 (and new claims 60-85).

Referring to new Claims 86-111, there was no expectation of success for the additional reason that the references do not disclose using the recited agent that alters at least one of "microtubule **polymerization and depolymerization**" (Claims 86-111), "microtubule **depolymerizing** protein" (Claim 93), and "**XKCM1**" (Claim 94). As to new Claims 112-124, neither of the references discloses the recited **stathmin** polypeptide. Since these limitations are **not** disclosed by any of the references, a logical argument cannot be made for a reasonable expectation of success in combining these limitation with labeled tubulin in the manner recited by the instant claims. Accordingly, new Claims 86-124 are not obvious.

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[31] (Emphasis added) Bonne *et al.*, page 2824, column 2, third paragraph.

[32] *In re Davies*, 475 F.2d 667, 670, 177 USPQ 381, 384 (CCPA 1973).

[33] (Emphasis added) Specification, page 27, lines 18-22.

5. Rejection of Claims 43-46 and 49-58 under 35 U.S.C. §103(a) over McNally & Vale in view of Balch (U.S. Patent No. 6,083,763)

Claims 43-46 and 49-58 stand rejected under 35 U.S.C. §103(a) for being allegedly obvious over McNally & Vale in view of Balch (U.S. Patent No. 6,083,763).[34] Applicants respectfully traverse because a *prima facie* case of obviousness has not been made.

i. The References Fail to Disclose All The Claims' Limitations

The Examiner **admitted** that McNally & Vale "do **not** teach that the disclosed method is performed in an array, which comprises a microliter plate and a multiplicity of at least 48 reaction mixtures wherein each reaction mixture comprises a distinct and distinguishable domain of said array with a plurality of agents."[35] Nonetheless, the Examiner argued that Balch provides the missing limitations since this reference discloses a multiplexed molecular analysis system.[36] The fact remains, however, that **none** of the references discloses labeling tubulin with the recited DAPI, ANS, bis-ANS, NPN, ruthernium red, cresol violet, and DCVJ (item E.4.i.) Accordingly, a *prima facie* case of obviousness must fail with respect to rejected Claims 43-46 and 49-58 (and new claims 60-85).

Applicants incorporate their arguments in E.4.i. with respect to the references' deficiency regarding new claims 60-124.

ii. Neither Motivation To Combine the Elements, Nor A Reasonable Expectation Of Success Is Established

The Examiner argued that "one of ordinary skill in the art would have been motivated to [utilize a multiplexed molecular analysis method] with a reasonable expectation of success by the teachings of the [Balch] patent because a multiplexed molecular analysis system can be

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[34] Paper No. 16, page 7, item 13.

[35] Paper No. 16, page 7, item 13.

[36] Paper No. 16, paragraph bridging pages 7 and 8.

advantageous due to the [*sic.*] commercially availability of reaction vessels . . ."[37] However, as discussed *supra* in items E.4.ii. and E.4.iii. (1) there is no motivation to label tubulin with DAPI, ANS, bis-ANS, NPN, ruthernium red, cresol violet, or DCVJ since these labels are **not** disclosed by any of the references in the first place, and (2) Applicants stated in the Specification that it was a "**surprising**" discovery that "the label does not interfere with the interaction of various test agents or cytoskeletal associated proteins with the labeled tubulin." Because all three (not just one) requirements of a *prima facie* case of obviousness are lacking, it is respectfully requested that the rejection of Claims 43-46 and 49-58 under 35 U.S.C. §103(a) be withdrawn.

Similarly, with respect to new Claims 60-124, both motivation and a reasonable expectation of success are lacking for the reasons discussed *supra* under items E.4.ii. and E.4.iii.

6. Rejection of Claims 43-46, 49-54 and 59 under 35 U.S.C. §103(a) over McNally & Vale

Claims 43-46, 49-54 and 59 have been rejected under 35 U.S.C. §103(a) for alleged obviousness over McNally & Vale.[38] Applicants respectfully disagree because a *prima facie* case of obviousness is lacking.

i. The References Fail to Disclose All The Claims' Limitations

The Examiner **admitted** that McNally & Vale "do **not** teach that the disclosed method further comprises listing the agents that alter microtubule polymerization, depolymerization, or severing into a database of therapeutic lead compounds that act on the cytoskeletal system."[39] This is not the only shortfall of the combined references since, as discussed *supra* in items E.4.ii. and E.4.iii., the references collectively fail to disclose the recited fluorescent labels. Accordingly, a *prima facie* case of obviousness cannot be made.

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[37] Paper No. 16, page 8, last paragraph.

[38] Paper No. 16, page 9, item 14.

[39] Paper No. 16, page 9, first full paragraph.

Similarly, with respect to new Claims 60-124, this prong is lacking for the reasons discussed supra under item E.4.ii. and E.4.iii.

ii. Motivation To Combine the Elements, And A Reasonable Expectation Of Success Are Not Established

The Examiner argued that one of ordinary skill in the art would have been "motivated to [generate a list of molecules] with a reasonable expectation of success because it would be convenient to provide a listing of agents." This is not enough to establish "motivation" or a "reasonable expectation of success" for the reasons discussed above in items 4.B., 4.C., and 5.B., which Applicants incorporate herein. In view of the above, it is respectfully requested that the rejection of Claims 43-46, 49-54 and 59 under 35 U.S.C. §103(a) be withdrawn.

With regard to new Claims 86-124, both motivation and a reasonable expectation of success are lacking for the reasons discussed *supra* under items 4.B. and 4.C.

7. Rejection of Claims 43-51 and 55-59 for obviousness-type double patenting over Application No. 09/724,595

Claims 43-51 and 55-59 have been provisionally rejected for obviousness-type double patenting over claims 43-71 of copending Application No. 09/724,595 (our docket No. UCSD-04868).[40] This rejection is moot in view of the enclosed abandonment of Application No. 09/724,595.

8. Rejection of Claims 43-51 and 55-59 for obviousness-type double patenting over Application No. 09/724,602

Claims 43-51 and 55-59 have been provisionally rejected for obviousness-type double patenting over claims 51 and 55-66 of copending Application No. 09/724,602 (our docket No. UCSD-04869).[41] This rejection is moot in view of the enclosed abandonment of Application No. 09/724,602.

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[40] Paper No. 16, page 10, item 16.

[41] Paper No. 16, page 11, item 17.

9. Rejection of Claims 11-16 for obviousness-type double patenting over Application No. 09/724,887

Claims 11-16 have been provisionally rejected for obviousness-type double patenting over claims 11-16 of copending Application No. 09/724,887 (our docket No. UCSD-04865).[42] This rejection is moot in view of the enclosed abandonment of Application No. 09/724,887.

10. Rejection of Claims 43-59 for double patenting under 35 U.S.C. § 101 over Application No. 09/724,596

Claims 43-59 have been provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as claims 43-59 of copending Application No. 09/724,596 (our docket No. UCSD-04867).[43] This rejection is moot in view of the enclosed abandonment of Application No. 09/724,596.

11. Rejection of Claims 1-10 for double patenting under 35 U.S.C. § 101 over Application No. 09/724,887

Claims 1-10 were provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as claims 1-10 of copending Application No. 09/724,887 (our docket No. UCSD-04865).[44] This rejection is moot in view of the enclosed abandonment of Application No. 09/724,887.

Please note that claims 1-10 in the instant application include within their scope the matter claimed in Claims 1-10 of abandoned Application No. 09/724,887.

CONCLUSION

All grounds of rejection and objection of the Office Action of December 3, 2002 having been addressed, reconsideration of the application is respectfully requested. To

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[42] Paper No. 16, page 12, item 18.

[43] Paper No. 16, page 13, item 20.

[44] Paper No. 16, page 13, item 21.

expedite prosecution, Applicants encourage the Examiner to call the undersigned at (415) 904-6500, **before beginning to draft another written communication,** if any.

Signed on behalf of:

Dated: July 17, 2003

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PATENT
Attorney Docket No. **UCSD-04765**

APPENDIX I

AMENDMENTS TO THE SPECIFICATION

Replace pages 1-47 of the originally-filed Specification with pages 1-60 of the clean copy of the Substitute Specification attached at Tab 2.

Renumber pages "48-66" of the Sequence listing to pages --61-79--.

PATENT
Attorney Docket No. **UCSD-04765**

APPENDIX II
AMENDMENTS TO THE CLAIMS

The following is a complete listing of all claims in the application. Status is in parenthetical expression, strike-through shows deleted matter, and underling shows added matter.

Renumber pages "67-85" to pages --80-98--.

1. (Currently Amended) A method of identifying ~~an~~ a test agent that modulates at least one activity selected from the group consisting of microtubule depolymerization, microtubule polymerization and microtubule severing, said method comprising the steps of:

(i) contacting a polymerized microtubule with at least one protein selected from the group consisting of a microtubule severing protein ~~or~~ and a microtubule depolymerizing protein, in the presence of ATP or GTP, and said test agent; and

(ii) detecting the formation of at least one product selected from the group consisting of tubulin monomers, dimers ~~or~~ and oligomers, wherein the formation of said tubulin monomers, dimers, or oligomers indicates that said test agent modulates microtubule depolymerization.

2. (Currently Amended) The method of claim 1, wherein said polymerized microtubule is labeled with 4'-6-diamidino-2-phenylindole (DAPI).

3. (Original) The method of claim 1, wherein said detecting is by fluorescent resonance energy transfer (FRET).

4. (Original) The method of claim 2, wherein said detecting, comprising detecting a change in fluorescence of said labeled microtubule.

5. (Original) The method of claim 1, wherein said detecting comprises centrifuging said tubulin monomers if present.

6. (Original) The method of claim 1, wherein said microtubules are stabilized by contact with an agent selected from the group consisting of paclitaxel, a paclitaxel analogue, and a non-hydrolyzable nucleotide GTP analogue.

7. (Original) The method of claim 1, wherein said microtubule is attached to a solid surface.

8. (Original) The method of claim 7, wherein said microtubule is attached to said surface by binding with an agent selected from the group consisting of an inactivated microtubule motor protein, an avidin-biotin linkage, an anti-tubulin antibody, a microtubule binding protein (MAP), and a polylysine.

9. (Currently Amended) The method of claim 1, wherein said ~~a~~ microtubule severing protein or ~~a~~ microtubule depolymerizing protein is selected from the group consisting of ~~a~~ katanin polypeptide, ~~a~~ p60 subunit of ~~a~~ katanin polypeptide, ~~an~~ *Xenopus* kinesin central motor 1 (XKCM1) polypeptide, and ~~a~~ stathmin (OP18) polypeptide.

10. (Currently Amended) The method of claim 9, wherein said microtubule severing protein is ~~a~~ katanin polypeptide or ~~a~~ p60 subunit of ~~a~~ katanin polypeptide.

11. (Currently Amended) The method of claim 10, wherein said p60 subunit of a katanin is a polypeptide ~~of claim 26~~ having microtubule severing activity, wherein said polypeptide comprises an isolated p60 subunit of katanin, and wherein said p60 subunit is encoded by a nucleic acid that hybridizes with a nucleic acid encoding the amino acid of SEQ ID NO:1, when incubated at 42°C overnight in 50% formamide.

12. (Original) The method of claim 10, wherein said p60 subunit is a polypeptide having the amino acid sequence of SEQ ID NO:1.

13. (Original) The method of claim 1, wherein said method is performed in an array where said array comprises a multiplicity of reaction mixtures, each reaction mixture

comprising a distinct and distinguishable domain of said array, and wherein said steps are performed in each reaction mixture.

14. (Original) The method of claim 13, wherein said array comprises a microtitre plate.

15. (Original) The method of claim 13, wherein said array comprises at least 48 of said reaction mixtures.

16. (Currently Amended) The method of claim 13, wherein said test agent is one of a plurality of test agents and wherein each reaction mixture comprises one test agent of said plurality of test agents.

17. (Currently Amended) A method of identifying a therapeutic lead compound that modulates at least one activity selected from the group consisting of depolymerization ~~or~~ , polymerization, and severing of a microtubule system, said method comprising the steps of:

i) providing an assay mixture comprising a katanin p60 subunit and a ~~microtubules~~ microtubule;

ii) contacting said assay mixture with a test ~~compound~~ agent to be screened for the ability to inhibit or enhance the microtubule severing or ATPase activity of said p60 subunit; and

iii) detecting at least one of specific binding of said test compound to said p60 subunit ~~or~~ and a change in the ATPase activity of said p60 subunit.

18. (Original) The method of claim 17, wherein said detecting comprises detecting ATPase activity utilizing malachite green as a detection reagent.

19. (Original) The method of claim 17, wherein said p60 subunit is labeled and said test agent is attached to a solid support.

20. (Original) The method of claim 17, wherein said test agent is labeled and said p60 subunit is attached to a solid support.

21. (Currently Amended) The method of claim 17, wherein said microtubules are stabilized by contact with an agent selected from the group consisting of paclitaxel, a paclitaxel analogue, and a non-hydrolyzable nucleotide GTP analogue.

22. (Original) The method of claim 17, wherein said method is performed in an array where said array comprises a multiplicity of reaction mixtures, each reaction mixture comprising a distinct and distinguishable domain of said array, and wherein said steps are performed in each reaction mixture.

23. (Original) The method of claim 22, wherein said array comprises a microtitre plate.

24. (Original) The method of claim 22, wherein said array comprises at least 48 of said reaction mixtures.

25. (Currently Amended) The method of claim 22, wherein said test agent comprises one of a plurality of test agents and wherein each reaction mixture comprises one test agent of said plurality of test agents.

Claims 26-42 (canceled)

43. (Currently Amended) A method of screening for ~~an~~ a test agent that alters microtubule ~~polymerization or depolymerization or~~ severing, said method comprising:

a) providing:

i) labeled tubulin, wherein the label of said labeled tubulin is selected from the group consisting of 4'-6-diamidino-2-phenylindol (DAPI), anilinonapthalene sulfonate (ANS), bis-ANS (Bis-anilinonapthalene sulfonate), N-phenyl-l-naphthylene

(NPN), ruthernium red, cresol violet, and 4-(dicyanovinyl)julolidine (DCVJ); and

ii) a test agent;

b) contacting said labeled tubulin with said test agent to produce contacted tubulin; and

c) comparing the fluorescence intensity or pattern of said contacted tubulin with the fluorescence intensity or pattern of labeled tubulin that is not contacted with said test agent, wherein a difference in fluorescence pattern or intensity between the contacted and the not contacted tubulin indicates that said test agent alters microtubule ~~polymerization or depolymerization~~ severing.

44. (Currently Amended) The method of claim 43, wherein said labeled tubulin is in at least one ~~the~~ form selected from the group consisting of tubulin monomers, tubulin dimers, ~~or~~ and tubulin oligomers.

45. (Original) The method of claim 43, wherein said labeled tubulin is in the form of a microtubule.

46. (Original) The method of claim 45, wherein said microtubule is attached to a solid surface.

47. (Cancelled).

48. (Currently Amended) The method of claim ~~47~~ 43, wherein said label is 4'-6-diamidino-2-phenylindole (DAPI).

49. (Original) The method of claim 46, wherein said microtubule is attached to said surface by binding with an agent selected from the group consisting of an inactivated microtubule motor protein, an avidin-biotin linkage, an anti-tubulin antibody, a microtubule binding protein (MAP), a polyarginine, a polyhistidine, and a polylysine.

50. (Currently Amended) The method of claim 43, wherein said contacting further comprises contacting said tubulin with a ~~microtubule-depolymerizing protein or a~~ microtubule severing protein.

51. (Currently Amended) The method of claim 50, wherein said ~~a~~ microtubule severing protein ~~or a microtubule depolymerizing protein~~ is selected from the group consisting of a katanin, and a p60 subunit of a katanin~~, an XKCM1, and a OP18 polypeptide~~.

52. (Currently Amended) The method of claim 51, wherein said microtubule severing protein is ~~a katanin or~~ a p60 subunit of a katanin.

53. (Currently Amended) The method of claim 52, wherein said p60 subunit of a katanin is a polypeptide ~~of claim 26~~ having microtubule severing activity, wherein said polypeptide comprises an isolated p60 subunit of katanin, and wherein said p60 subunit is encoded by a nucleic acid that hybridizes with a nucleic acid encoding the amino acid of SEQ ID NO:1, when incubated at 42°C overnight in 50% formamide.

54. (Original) The method of claim 52, wherein said p60 subunit is a polypeptide having the amino acid sequence of SEQ ID NO:1.

55. (Currently Amended) The method of claim 43, wherein said method is performed in an array where said array comprises a multiplicity of reaction mixtures~~, each reaction mixture comprising a distinct and distinguishable domain of said array~~, and wherein said steps are performed in each reaction mixture.

56. (Original) The method of claim 55, wherein said array comprises a microtitre plate.

57. (Original) The method of claim 55, wherein said array comprises at least 48 of said reaction mixtures.

58. (Currently Amended) The method of claim 55, wherein said test agent ~~one of~~ comprises a plurality of test agents and wherein each reaction mixture comprises one test agent of said plurality of test agents.

59. (Currently Amended) The method of claim 43, further comprising listing the test agents that alters microtubule ~~polymerization, depolymerization, or~~ severing into a database of therapeutic lead compounds that act on the cytoskeletal system.

60. (New) A method of screening for a test agent that alters at least one activity selected from the group consisting of microtubule polymerization, microtubule depolymerization, and microtubule severing, said method comprising:

a) providing:
   i) labeled tubulin,
   ii) an isolated polypeptide having at least one activity selected from the group consisting of microtubule polymerization activity, microtubule depolymerization activity, and microtubule severing activity, said polypeptide comprising a katanin p60 subunit, and
   iii) a test agent;

b) contacting said labeled tubulin with said isolated polypeptide and with said test agent to produce contacted tubulin; and

c) comparing the fluorescence intensity or pattern of said contacted tubulin with the fluorescence intensity or pattern of labeled tubulin that is not contacted with said polypeptide and said test agent, wherein a difference in fluorescence pattern or intensity between the contacted and the not contacted tubulin indicates that said test agent alters at least one activity selected from the group consisting of microtubule polymerization, microtubule depolymerization, and microtubule severing.

61. (New) The method of Claim 60, wherein said labeled tubulin is in at least one form selected from the group consisting of tubulin monomers, tubulin dimers, and tubulin oligomers.

62. (New) The method of Claim 60, wherein said labeled tubulin is in the form of a microtubule.

63. (New) The method of Claim 62, wherein said microtubule is attached to a solid surface.

64. (New) The method of Claim 63, wherein said microtubule is attached to said surface by binding with a molecule selected from the group consisting of an inactivated microtubule motor protein, an avidin-biotin linkage, an anti-tubulin antibody, a microtubule binding protein (MAP), a polyarginine, a polyhistidine, and a polylysine.

65. (New) The method of Claim 62, wherein the label of said labeled tubulin is selected from the group consisting of 4'-6-diamidino-2-phenylindole (DAPI), anilinonapthalene sulfonate (ANS), bis-ANS (Bis-anilinonapthalene sulfonate), N-phenyl-1-naphthylene (NPN), ruthernium red, cresol violet, and 4-(dicyanovinyl)julolidine (DCVJ).

66. (New) The method of Claim 62, wherein the label of said labeled tubulin is 4'-6-diamidino-2-phenylindole (DAPI).

67. (New) The method of Claim 60, wherein said katanin p60 subunit is recombinant.

68. (New) The method of Claim 60, wherein said katanin p60 subunit has the amino acid sequence of SEQ ID NO:1.

69. (New) The method of Claim 60, wherein said method is performed in an array, wherein said array comprises a multiplicity of reaction mixtures.

70. (New) The method of Claim 69, wherein said array comprises a microtitre plate.

71. (New) The method of Claim 69, wherein said array comprises at least 48 of said reaction mixtures.

72. (New) The method of Claim 60, further comprising step d) listing the test agents that alter at least one of microtubule polymerization, microtubule depolymerization, and microtubule severing into a database.

73. (New) A method of screening for a test agent that alters at least one activity selected from the group consisting of microtubule polymerization, microtubule depolymerization, and microtubule severing, said method comprising:

a) providing:
   i) labeled tubulin,
   ii) an isolated katanin p60 subunit, and
   iii) a test agent;

b) contacting said labeled tubulin with said isolated katanin p60 subunit and with said test agent to produce contacted tubulin; and

c) comparing the fluorescence intensity or pattern of said contacted tubulin with the fluorescence intensity or pattern of labeled tubulin that is not contacted with said polypeptide and said test agent, wherein a difference in fluorescence pattern or intensity between the contacted and the not contacted tubulin indicates that said test agent alters at least one activity selected from the group consisting of microtubule polymerization, microtubule depolymerization, and microtubule severing.

74. (New) The method of Claim 73, wherein said labeled tubulin is in at least one form selected from the group consisting of tubulin monomers, tubulin dimers, and tubulin oligomers.

75. (New) The method of Claim 73, wherein said labeled tubulin is in the form of a microtubule.

76. (New) The method of Claim 75, wherein said microtubule is attached to a solid surface.

77. (New) The method of Claim 76, wherein said microtubule is attached to said surface by binding with a molecule selected from the group consisting of an inactivated microtubule motor protein, an avidin-biotin linkage, an anti-tubulin antibody, a microtubule binding protein (MAP), a polyarginine, a polyhistidine, and a polylysine.

78. (New) The method of Claim 75, wherein the label of said labeled tubulin is selected from the group consisting of 4'-6-diamidino-2-phenylindole (DAPI), anilinonapthalene sulfonate (ANS), bis-ANS (Bis-anilinonapthalene sulfonate), N-phenyl-l-naphthylene (NPN), ruthernium red, cresol violet, and 4-(dicyanovinyl)julolidine (DCVJ).

79. (New) The method of Claim 75, wherein the label of said labeled tubulin is 4'-6-diamidino-2-phenylindole (DAPI).

80. (New) The method of Claim 73, wherein said katanin p60 subunit is recombinant.

81. (New) The method of Claim 73, wherein said katanin p60 subunit has the amino acid sequence of SEQ ID NO:1.

82. (New) The method of Claim 73, wherein said method is performed in an array, wherein said array comprises a multiplicity of reaction mixtures.

83. (New) The method of Claim 82, wherein said array comprises a microtitre plate.

84. (New) The method of Claim 82, wherein said array comprises at least 48 of said reaction mixtures.

85. (New) The method of Claim 73, further comprising step d) listing the test agents that alter at least one of microtubule polymerization, microtubule depolymerization, and microtubule severing into a database.

86. (New) A method of screening for a test agent that alters at least one activity selected from the group consisting of microtubule polymerization and depolymerization, said method comprising:

a) providing labeled tubulin;

b) contacting said labeled tubulin with said test agent to produce contacted tubulin; and

c) comparing the fluorescence intensity or pattern of said contacted tubulin with the fluorescence intensity or pattern of labeled tubulin that is not contacted with said test agent wherein a difference in fluorescence pattern or intensity between the contacted and the not contacted tubulin indicates that said test agent alters at least one activity selected from the group consisting of microtubule polymerization and depolymerization.

87. (New) The method of claim 86, wherein said labeled tubulin is in at least one form selected from the group consisting of tubulin monomers, tubulin dimers, and tubulin oligomers.

88. (New) The method of claim 86, wherein said labeled tubulin is in the form of a microtubule.

89. (New) The method of claim 88, wherein said microtubule is attached to a solid surface.

90. (New) The method of claim 88, wherein the label of said labeled tubulin is selected from the group consisting of 4'-6-diamidino-2-phenylindole (DAPI), anilinonapthalene sulfonate (ANS), bis-ANS (Bis-anilinonapthalene sulfonate),

N-phenyl-l-naphthylene (NPN), ruthernium red, cresol violet, and 4-(dicyanovinyl)julolidine (DCVJ).

91. (New) The method of claim 90, wherein said label is 4'-6-diamidino-2-phenylindole (DAPI).

92. (New) The method of claim 89, wherein said microtubule is attached to said surface by binding with an agent selected from the group consisting of an inactivated microtubule motor protein, an avidin-biotin linkage, an anti-tubulin antibody, a microtubule binding protein (MAP), a polyarginine, a polyhistidine, and a polylysine.

93. (New) A method of screening for a test agent that alters at least one activity selected from the group consisting of microtubule polymerization and depolymerization, said method comprising:

a) providing:
   i) labeled tubulin,
   ii) a microtubule depolymerizing protein, and
   iii) a test agent;

b) contacting said tubulin with said microtubule depolymerizing protein and with said test agent to produce contacted tubulin; and

c) comparing the fluorescence intensity or pattern of said contacted tubulin with the fluorescence intensity or pattern of labeled tubulin that is not contacted with said test agent, wherein a difference in fluorescence pattern or intensity between the contacted and the not contacted tubulin indicates that said test agent alters at least one activity selected from the group consisting of microtubule polymerization and depolymerization.

94. (New) The method of claim 93, wherein said microtubule depolymerizing protein comprises a *Xenopus* kinesin central motor 1 (XKCM1) polypeptide.

95. (New) The method of claim 86, wherein said method is performed in an array where said array comprises a multiplicity of reaction mixtures, and wherein said steps are performed in each reaction mixture.

96. (New) The method of claim 95, wherein said array comprises a microtitre plate.

97. (New) The method of claim 95, wherein said array comprises at least 48 of said reaction mixtures.

98. (New) The method of claim 95, wherein said test agent comprises a plurality of test agents and wherein each reaction mixture comprises one test agent of said plurality of test agents.

99. (New) The method of claim 86, further comprising listing the test agents that alter at least one of microtubule polymerization and depolymerization into a database of therapeutic lead compounds that act on the cytoskeletal system.

100. (New) The method of claim 93, wherein said labeled tubulin is in at least one form selected from the group consisting of tubulin monomers, tubulin dimers, and tubulin oligomers.

101. (New) The method of claim 93, wherein said labeled tubulin is in the form of a microtubule.

102. (New) The method of claim 101, wherein said microtubule is attached to a solid surface.

103. (New) The method of claim 101, wherein the label of said labeled tubulin is selected from the group consisting of 4'-6-diamidino-2-phenylindole (DAPI), anilinonapthalene sulfonate (ANS), bis-ANS (Bis-anilinonapthalene sulfonate),

N-phenyl-l-naphthylene (NPN), ruthernium red, cresol violet, and 4-(dicyanovinyl)julolidine (DCVJ).

104. (New) The method of claim 103, wherein said label is 4'-6-diamidino-2-phenylindole (DAPI).

105. (New) The method of claim 102, wherein said microtubule is attached to said surface by binding with an agent selected from the group consisting of an inactivated microtubule motor protein, an avidin-biotin linkage, an anti-tubulin antibody, a microtubule binding protein (MAP), a polyarginine, a polyhistidine, and a polylysine.

106. (New) The method of claim 93, wherein said method is performed in an array, wherein said array comprises a multiplicity of reaction mixtures, and wherein said steps are performed in each reaction mixture.

107. (New) The method of claim 106, wherein said array comprises a microtitre plate.

108. (New) The method of claim 106, wherein said array comprises at least 48 of said reaction mixtures.

109. (New) The method of claim 106, wherein said test agent comprises a plurality of test agents, and wherein each reaction mixture comprises one test agent of said plurality of test agents.

110. (New) The method of claim 93, further comprising listing the test agents that alter at least one of microtubule polymerization and depolymerization into a database of therapeutic lead compounds that act on the cytoskeletal system.

111. (New) The method of claim 93, wherein said microtubule depolymerizing protein is a *Xenopus* kinesin central motor 1 (XKCM1) polypeptide.

112. (New) A method of screening for a test agent that alters at least one activity selected from the group consisting of microtubule polymerization and depolymerization, said method comprising:

a) providing:

i) labeled tubulin,

ii) a microtubule depolymerizing protein comprising a stathmin polypeptide, and

iii) a test agent;

b) contacting said labeled tubulin with said microtubule depolymerizing protein and with said test agent to produce contacted tubulin; and

c) comparing the fluorescence intensity or pattern of said contacted tubulin with the fluorescence intensity or pattern of labeled tubulin that is not contacted with said test agent, wherein a difference in fluorescence pattern or intensity between the contacted and the not contacted tubulin indicates that said test agent alters at least one activity selected from the group consisting of microtubule polymerization and depolymerization.

113. (New) The method of claim 112, wherein said method is performed in an array where said array comprises a multiplicity of reaction mixtures, and wherein said steps are performed in each reaction mixture.

114. (New) The method of claim 113, wherein said array comprises a microtitre plate.

115. (New) The method of claim 113, wherein said array comprises at least 48 of said reaction mixtures.

116. (New) The method of claim 113, wherein said test agent comprises a plurality of test agents and wherein each reaction mixture comprises one test agent of said plurality of test agents.

117. (New) The method of claim 112, further comprising listing the test agents that alter at least one of microtubule polymerization and depolymerization into a database of therapeutic lead compounds that act on the cytoskeletal system.

118. (New) The method of claim 112, wherein said labeled tubulin is in at least one form selected from the group consisting of tubulin monomers, tubulin dimers, and tubulin oligomers.

119. (New) The method of claim 112, wherein said labeled tubulin is in the form of a microtubule.

120. (New) The method of claim 119, wherein said microtubule is attached to a solid surface.

121. (New) The method of claim 119, wherein the label of said labeled tubulin is selected from the group consisting of 4'-6-diamidino-2-phenylindole (DAPI), anilinonapthalene sulfonate (ANS), bis-ANS (Bis-anilinonapthalene sulfonate), N-phenyl-l-naphthylene (NPN), ruthernium red, cresol violet, and 4-(dicyanovinyl)julolidine (DCVJ).

122. (New) The method of claim 121, wherein said label is 4'-6-diamidino-2-phenylindole (DAPI).

123. (New) The method of claim 120, wherein said microtubule is attached to said surface by binding with an agent selected from the group consisting of an inactivated microtubule motor protein, an avidin-biotin linkage, an anti-tubulin antibody, a microtubule binding protein (MAP), a polyarginine, a polyhistidine, and a polylysine.

124. (New) The method of claim 112, wherein said microtubule depolymerizing protein is a stathmin polypeptide.

PATENT
Attorney Docket No. **UCSD-04765**

APPENDIX III
CURRENTLY PENDING CLAIMS

The following is a clean version of the list of pending claims following entry of the instant amendment.

1. (Currently Amended) A method of identifying a test agent that modulates at least one activity selected from the group consisting of microtubule depolymerization, microtubule polymerization and microtubule severing, said method comprising the steps of:

(i) contacting a polymerized microtubule with at least one protein selected from the group consisting of a microtubule severing protein and a microtubule depolymerizing protein, in the presence of ATP or GTP, and said test agent; and

(ii) detecting the formation of at least one product selected from the group consisting of tubulin monomers, dimers and oligomers, wherein the formation of said tubulin monomers, dimers, or oligomers indicates that said test agent modulates microtubule depolymerization.

2. (Currently Amended) The method of claim 1, wherein said polymerized microtubule is labeled with 4'-6-diamidino-2-phenylindole (DAPI).

3. (Original) The method of claim 1, wherein said detecting is by fluorescent resonance energy transfer (FRET).

4. (Original) The method of claim 2, wherein said detecting, comprising detecting a change in fluorescence of said labeled microtubule.

5. (Original) The method of claim 1, wherein said detecting comprises centrifuging said tubulin monomers if present.

6. (Original) The method of claim 1, wherein said microtubules are stabilized by contact with an agent selected from the group consisting of paclitaxel, a paclitaxel analogue, and a non-hydrolyzable nucleotide GTP analogue.

7. (Original) The method of claim 1, wherein said microtubule is attached to a solid surface.

8. (Original) The method of claim 7, wherein said microtubule is attached to said surface by binding with an agent selected from the group consisting of an inactivated microtubule motor protein, an avidin-biotin linkage, an anti-tubulin antibody, a microtubule binding protein (MAP), and a polylysine.

9. (Currently Amended) The method of claim 1, wherein said microtubule severing protein or microtubule depolymerizing protein is selected from the group consisting of katanin polypeptide, p60 subunit of katanin polypeptide, *Xenopus* kinesin central motor 1 (XKCM1) polypeptide, and stathmin (OP18) polypeptide.

10. (Currently Amended) The method of claim 9, wherein said microtubule severing protein is katanin polypeptide or p60 subunit of katanin polypeptide.

11. (Currently Amended) The method of claim 10, wherein said p60 subunit of a katanin is a polypeptide having microtubule severing activity, wherein said polypeptide comprises an isolated p60 subunit of katanin, and wherein said p60 subunit is encoded by a nucleic acid that hybridizes with a nucleic acid encoding the amino acid of SEQ ID NO:1, when incubated at 42°C overnight in 50% formamide.

12. (Original) The method of claim 10, wherein said p60 subunit is a polypeptide having the amino acid sequence of SEQ ID NO:1.

13. (Original) The method of claim 1, wherein said method is performed in an array where said array comprises a multiplicity of reaction mixtures, each reaction mixture

comprising a distinct and distinguishable domain of said array, and wherein said steps are performed in each reaction mixture.

14. (Original) The method of claim 13, wherein said array comprises a microtitre plate.

15. (Original) The method of claim 13, wherein said array comprises at least 48 of said reaction mixtures.

16. (Currently Amended) The method of claim 13, wherein said test agent is one of a plurality of test agents and wherein each reaction mixture comprises one test agent of said plurality of test agents.

17. (Currently Amended) A method of identifying a therapeutic lead compound that modulates at least one activity selected from the group consisting of depolymerization, polymerization, and severing of a microtubule system, said method comprising the steps of:

i) providing an assay mixture comprising a katanin p60 subunit and a microtubule;

ii) contacting said assay mixture with a test agent to be screened for the ability to inhibit or enhance the microtubule severing or ATPase activity of said p60 subunit; and

iii) detecting at least one of specific binding of said test compound to said p60 subunit and a change in the ATPase activity of said p60 subunit.

18. (Original) The method of claim 17, wherein said detecting comprises detecting ATPase activity utilizing malachite green as a detection reagent.

19. (Original) The method of claim 17, wherein said p60 subunit is labeled and said test agent is attached to a solid support.

20. (Original) The method of claim 17, wherein said test agent is labeled and said p60 subunit is attached to a solid support.

21. (Currently Amended) The method of claim 17, wherein said microtubules are stabilized by contact with an agent selected from the group consisting of paclitaxel, a paclitaxel analogue, and a non-hydrolyzable nucleotide GTP analogue.

22. (Original) The method of claim 17, wherein said method is performed in an array where said array comprises a multiplicity of reaction mixtures, each reaction mixture comprising a distinct and distinguishable domain of said array, and wherein said steps are performed in each reaction mixture.

23. (Original) The method of claim 22, wherein said array comprises a microtitre plate.

24. (Original) The method of claim 22, wherein said array comprises at least 48 of said reaction mixtures.

25. (Currently Amended) The method of claim 22, wherein said test agent comprises one of a plurality of test agents and wherein each reaction mixture comprises one test agent of said plurality of test agents.

Claims 26-42 (canceled)

43. (Currently Amended) A method of screening for a test agent that alters microtubule severing, said method comprising:

a) providing:

i) labeled tubulin, wherein the label of said labeled tubulin is selected from the group consisting of 4'-6-diamidino-2-phenylindole (DAPI), anilinonapthalene sulfonate (ANS), bis-ANS (Bis-anilinonapthalene sulfonate), N-phenyl-l-naphthylene

(NPN), ruthernium red, cresol violet, and 4-(dicyanovinyl)julolidine (DCVJ); and

ii) a test agent;

b) contacting said labeled tubulin with said test agent to produce contacted tubulin; and

c) comparing the fluorescence intensity or pattern of said contacted tubulin with the fluorescence intensity or pattern of labeled tubulin that is not contacted with said test agent, wherein a difference in fluorescence pattern or intensity between the contacted and the not contacted tubulin indicates that said test agent alters microtubule severing.

44. (Currently Amended) The method of claim 43, wherein said labeled tubulin is in at least one form selected from the group consisting of tubulin monomers, tubulin dimers, and tubulin oligomers.

45. (Original) The method of claim 43, wherein said labeled tubulin is in the form of a microtubule.

46. (Original) The method of claim 45, wherein said microtubule is attached to a solid surface.

47. (Cancelled).

48. (Currently Amended) The method of claim 43, wherein said label is 4'-6-diamidino-2-phenylindole (DAPI).

49. (Original) The method of claim 46, wherein said microtubule is attached to said surface by binding with an agent selected from the group consisting of an inactivated microtubule motor protein, an avidin-biotin linkage, an anti-tubulin antibody, a microtubule binding protein (MAP), a polyarginine, a polyhistidine, and a polylysine.

50. (Currently Amended) The method of claim 43, wherein said contacting further comprises contacting said tubulin with a microtubule severing protein.

51. (Currently Amended) The method of claim 50, wherein said microtubule severing protein is selected from the group consisting of a katanin, and a p60 subunit of a katanin.

52. (Currently Amended) The method of claim 51, wherein said microtubule severing protein is a p60 subunit of a katanin.

53. (Currently Amended) The method of claim 52, wherein said p60 subunit of a katanin is a polypeptide having microtubule severing activity, wherein said polypeptide comprises an isolated p60 subunit of katanin, and wherein said p60 subunit is encoded by a nucleic acid that hybridizes with a nucleic acid encoding the amino acid of SEQ ID NO:1, when incubated at 42°C overnight in 50% formamide.

54. (Original) The method of claim 52, wherein said p60 subunit is a polypeptide having the amino acid sequence of SEQ ID NO:1.

55. (Currently Amended) The method of claim 43, wherein said method is performed in an array where said array comprises a multiplicity of reaction mixtures, and wherein said steps are performed in each reaction mixture.

56. (Original) The method of claim 55, wherein said array comprises a microtitre plate.

57. (Original) The method of claim 55, wherein said array comprises at least 48 of said reaction mixtures.

58. (Currently Amended) The method of claim 55, wherein said test agent comprises a plurality of test agents and wherein each reaction mixture comprises one test agent of said plurality of test agents.

59. (Currently Amended) The method of claim 43, further comprising listing the test agents that alter microtubule severing into a database of therapeutic lead compounds that act on the cytoskeletal system.

60. (New) A method of screening for a test agent that alters at least one activity selected from the group consisting of microtubule polymerization, microtubule depolymerization, and microtubule severing, said method comprising:

a) providing:
   i) labeled tubulin,
   ii) an isolated polypeptide having at least one activity selected from the group consisting of microtubule polymerization activity, microtubule depolymerization activity, and microtubule severing activity, said polypeptide comprising a katanin p60 subunit, and
   iii) a test agent;

b) contacting said labeled tubulin with said isolated polypeptide and with said test agent to produce contacted tubulin; and

c) comparing the fluorescence intensity or pattern of said contacted tubulin with the fluorescence intensity or pattern of labeled tubulin that is not contacted with said polypeptide and said test agent, wherein a difference in fluorescence pattern or intensity between the contacted and the not contacted tubulin indicates that said test agent alters at least one activity selected from the group consisting of microtubule polymerization, microtubule depolymerization, and microtubule severing.

61. (New) The method of Claim 60, wherein said labeled tubulin is in at least one form selected from the group consisting of tubulin monomers, tubulin dimers, and tubulin oligomers.

62. (New) The method of Claim 60, wherein said labeled tubulin is in the form of a microtubule.

63. (New) The method of Claim 62, wherein said microtubule is attached to a solid surface.

64. (New) The method of Claim 63, wherein said microtubule is attached to said surface by binding with a molecule selected from the group consisting of an inactivated microtubule motor protein, an avidin-biotin linkage, an anti-tubulin antibody, a microtubule binding protein (MAP), a polyarginine, a polyhistidine, and a polylysine.

65. (New) The method of Claim 62, wherein the label of said labeled tubulin is selected from the group consisting of 4'-6-diamidino-2-phenylindole (DAPI), anilinonapthalene sulfonate (ANS), bis-ANS (Bis-anilinonapthalene sulfonate), N-phenyl-1-naphthylene (NPN), ruthernium red, cresol violet, and 4-(dicyanovinyl)julolidine (DCVJ).

66. (New) The method of Claim 62, wherein the label of said labeled tubulin is 4'-6-diamidino-2-phenylindole (DAPI).

67. (New) The method of Claim 60, wherein said katanin p60 subunit is recombinant.

68. (New) The method of Claim 60, wherein said katanin p60 subunit has the amino acid sequence of SEQ ID NO:1.

69. (New) The method of Claim 60, wherein said method is performed in an array, wherein said array comprises a multiplicity of reaction mixtures.

70. (New) The method of Claim 69, wherein said array comprises a microtitre plate.

71. (New) The method of Claim 69, wherein said array comprises at least 48 of said reaction mixtures.

72. (New) The method of Claim 60, further comprising step d) listing the test agents that alter at least one of microtubule polymerization, microtubule depolymerization, and microtubule severing into a database.

73. (New) A method of screening for a test agent that alters at least one activity selected from the group consisting of microtubule polymerization, microtubule depolymerization, and microtubule severing, said method comprising:

a) providing:
   i) labeled tubulin,
   ii) an isolated katanin p60 subunit, and
   iii) a test agent;
b) contacting said labeled tubulin with said isolated katanin p60 subunit and with said test agent to produce contacted tubulin; and
c) comparing the fluorescence intensity or pattern of said contacted tubulin with the fluorescence intensity or pattern of labeled tubulin that is not contacted with said polypeptide and said test agent, wherein a difference in fluorescence pattern or intensity between the contacted and the not contacted tubulin indicates that said test agent alters at least one activity selected from the group consisting of microtubule polymerization, microtubule depolymerization, and microtubule severing.

74. (New) The method of Claim 73, wherein said labeled tubulin is in at least one form selected from the group consisting of tubulin monomers, tubulin dimers, and tubulin oligomers.

75. (New) The method of Claim 73, wherein said labeled tubulin is in the form of a microtubule.

76. (New) The method of Claim 75, wherein said microtubule is attached to a solid surface.

77. (New) The method of Claim 76, wherein said microtubule is attached to said surface by binding with a molecule selected from the group consisting of an inactivated microtubule motor protein, an avidin-biotin linkage, an anti-tubulin antibody, a microtubule binding protein (MAP), a polyarginine, a polyhistidine, and a polylysine.

78. (New) The method of Claim 75, wherein the label of said labeled tubulin is selected from the group consisting of 4'-6-diamidino-2-phenylindole (DAPI), anilinonapthalene sulfonate (ANS), bis-ANS (Bis-anilinonapthalene sulfonate), N-phenyl-l-naphthylene (NPN), ruthernium red, cresol violet, and 4-(dicyanovinyl)julolidine (DCVJ).

79. (New) The method of Claim 75, wherein the label of said labeled tubulin is 4'-6-diamidino-2-phenylindole (DAPI).

80. (New) The method of Claim 73, wherein said katanin p60 subunit is recombinant.

81. (New) The method of Claim 73, wherein said katanin p60 subunit has the amino acid sequence of SEQ ID NO:1.

82. (New) The method of Claim 73, wherein said method is performed in an array, wherein said array comprises a multiplicity of reaction mixtures.

83. (New) The method of Claim 82, wherein said array comprises a microtitre plate.

84. (New) The method of Claim 82, wherein said array comprises at least 48 of said reaction mixtures.

85. (New) The method of Claim 73, further comprising step d) listing the test agents that alter at least one of microtubule polymerization, microtubule depolymerization, and microtubule severing into a database.

86. (New) A method of screening for a test agent that alters at least one activity selected from the group consisting of microtubule polymerization and depolymerization, said method comprising:

a) providing labeled tubulin;

b) contacting said labeled tubulin with said test agent to produce contacted tubulin; and

c) comparing the fluorescence intensity or pattern of said contacted tubulin with the fluorescence intensity or pattern of labeled tubulin that is not contacted with said test agent wherein a difference in fluorescence pattern or intensity between the contacted and the not contacted tubulin indicates that said test agent alters at least one activity selected from the group consisting of microtubule polymerization and depolymerization.

87. (New) The method of claim 86, wherein said labeled tubulin is in at least one form selected from the group consisting of tubulin monomers, tubulin dimers, and tubulin oligomers.

88. (New) The method of claim 86, wherein said labeled tubulin is in the form of a microtubule.

89. (New) The method of claim 88, wherein said microtubule is attached to a solid surface.

90. (New) The method of claim 88, wherein the label of said labeled tubulin is selected from the group consisting of 4'-6-diamidino-2-phenylindole (DAPI), anilinonapthalene sulfonate (ANS), bis-ANS (Bis-anilinonapthalene sulfonate),

N-phenyl-l-naphthylene (NPN), ruthernium red, cresol violet, and 4-(dicyanovinyl)julolidine (DCVJ).

91. (New) The method of claim 90, wherein said label is 4'-6-diamidino-2-phenylindole (DAPI).

92. (New) The method of claim 89, wherein said microtubule is attached to said surface by binding with an agent selected from the group consisting of an inactivated microtubule motor protein, an avidin-biotin linkage, an anti-tubulin antibody, a microtubule binding protein (MAP), a polyarginine, a polyhistidine, and a polylysine.

93. (New) A method of screening for a test agent that alters at least one activity selected from the group consisting of microtubule polymerization and depolymerization, said method comprising:

a) providing:
   i) labeled tubulin,
   ii) a microtubule depolymerizing protein, and
   iii) a test agent;
b) contacting said tubulin with said microtubule depolymerizing protein and with said test agent to produce contacted tubulin; and
c) comparing the fluorescence intensity or pattern of said contacted tubulin with the fluorescence intensity or pattern of labeled tubulin that is not contacted with said test agent, wherein a difference in fluorescence pattern or intensity between the contacted and the not contacted tubulin indicates that said test agent alters at least one activity selected from the group consisting of microtubule polymerization and depolymerization.

94. (New) The method of claim 93, wherein said microtubule depolymerizing protein comprises a *Xenopus* kinesin central motor 1 (XKCM1) polypeptide.

95. (New) The method of claim 86, wherein said method is performed in an array where said array comprises a multiplicity of reaction mixtures, and wherein said steps are performed in each reaction mixture.

96. (New) The method of claim 95, wherein said array comprises a microtitre plate.

97. (New) The method of claim 95, wherein said array comprises at least 48 of said reaction mixtures.

98. (New) The method of claim 95, wherein said test agent comprises a plurality of test agents and wherein each reaction mixture comprises one test agent of said plurality of test agents.

99. (New) The method of claim 86, further comprising listing the test agents that alter at least one of microtubule polymerization and depolymerization into a database of therapeutic lead compounds that act on the cytoskeletal system.

100. (New) The method of claim 93, wherein said labeled tubulin is in at least one form selected from the group consisting of tubulin monomers, tubulin dimers, and tubulin oligomers.

101. (New) The method of claim 93, wherein said labeled tubulin is in the form of a microtubule.

102. (New) The method of claim 101, wherein said microtubule is attached to a solid surface.

103. (New) The method of claim 101, wherein the label of said labeled tubulin is selected from the group consisting of 4'-6-diamidino-2-phenylindole (DAPI), anilinonapthalene sulfonate (ANS), bis-ANS (Bis-anilinonapthalenc sulfonate),

N-phenyl-1-naphthylene (NPN), ruthernium red, cresol violet, and 4-(dicyanovinyl)julolidine (DCVJ).

104. (New) The method of claim 103, wherein said label is 4'-6-diamidino-2-phenylindole (DAPI).

105. (New) The method of claim 102, wherein said microtubule is attached to said surface by binding with an agent selected from the group consisting of an inactivated microtubule motor protein, an avidin-biotin linkage, an anti-tubulin antibody, a microtubule binding protein (MAP), a polyarginine, a polyhistidine, and a polylysine.

106. (New) The method of claim 93, wherein said method is performed in an array, wherein said array comprises a multiplicity of reaction mixtures, and wherein said steps are performed in each reaction mixture.

107. (New) The method of claim 106, wherein said array comprises a microtitre plate.

108. (New) The method of claim 106, wherein said array comprises at least 48 of said reaction mixtures.

109. (New) The method of claim 106, wherein said test agent comprises a plurality of test agents, and wherein each reaction mixture comprises one test agent of said plurality of test agents.

110. (New) The method of claim 93, further comprising listing the test agents that alter at least one of microtubule polymerization and depolymerization into a database of therapeutic lead compounds that act on the cytoskeletal system.

111. (New) The method of claim 93, wherein said microtubule depolymerizing protein is a *Xenopus* kinesin central motor 1 (XKCM1) polypeptide.

112. (New) A method of screening for a test agent that alters at least one activity selected from the group consisting of microtubule polymerization and depolymerization, said method comprising:

a) providing:

i) labeled tubulin,

ii) a microtubule depolymerizing protein comprising a stathmin polypeptide, and

iii) a test agent;

b) contacting said labeled tubulin with said microtubule depolymerizing protein and with said test agent to produce contacted tubulin; and

c) comparing the fluorescence intensity or pattern of said contacted tubulin with the fluorescence intensity or pattern of labeled tubulin that is not contacted with said test agent, wherein a difference in fluorescence pattern or intensity between the contacted and the not contacted tubulin indicates that said test agent alters at least one activity selected from the group consisting of microtubule polymerization and depolymerization.

113. (New) The method of claim 112, wherein said method is performed in an array where said array comprises a multiplicity of reaction mixtures, and wherein said steps are performed in each reaction mixture.

114. (New) The method of claim 113, wherein said array comprises a microtitre plate.

115. (New) The method of claim 113, wherein said array comprises at least 48 of said reaction mixtures.

116. (New) The method of claim 113, wherein said test agent comprises a plurality of test agents and wherein each reaction mixture comprises one test agent of said plurality of test agents.

117. (New) The method of claim 112, further comprising listing the test agents that alter at least one of microtubule polymerization and depolymerization into a database of therapeutic lead compounds that act on the cytoskeletal system.

118. (New) The method of claim 112, wherein said labeled tubulin is in at least one form selected from the group consisting of tubulin monomers, tubulin dimers, and tubulin oligomers.

119. (New) The method of claim 112, wherein said labeled tubulin is in the form of a microtubule.

120. (New) The method of claim 119, wherein said microtubule is attached to a solid surface.

121. (New) The method of claim 119, wherein the label of said labeled tubulin is selected from the group consisting of 4'-6-diamidino-2-phenylindole (DAPI), anilinonapthalene sulfonate (ANS), bis-ANS (Bis-anilinonapthalene sulfonate), N-phenyl-l-naphthylene (NPN), ruthernium red, cresol violet, and 4-(dicyanovinyl)julolidine (DCVJ).

122. (New) The method of claim 121, wherein said label is 4'-6-diamidino-2-phenylindole (DAPI).

123. (New) The method of claim 120, wherein said microtubule is attached to said surface by binding with an agent selected from the group consisting of an inactivated microtubule motor protein, an avidin-biotin linkage, an anti-tubulin antibody, a microtubule binding protein (MAP), a polyarginine, a polyhistidine, and a polylysine.

124. (New) The method of claim 112, wherein said microtubule depolymerizing protein is a stathmin polypeptide.